

Regulatory Determinations Support Document for Selected Contaminants from the Second Drinking Water Contaminant Candidate List (CCL 2)

Part III: What About the Remaining CCL 2 Contaminants?

As stated in Chapter 1, EPA is only making regulatory determinations on CCL 2 contaminants that have sufficient information to support a regulatory determination at this time. EPA is not able to make a preliminary determination for perchlorate at this time, because in order to evaluate perchlorate against the three statutory criteria, the Agency believes additional information may be needed to more fully characterize perchlorate exposure and determine whether regulating perchlorate in drinking water presents a meaningful opportunity for health risk reduction. For the 30 remaining chemicals and the 9 microbial pathogens, the Agency lacks adequate information in the areas of health effects or occurrence or both.

The Agency continues to conduct research and/or to collect information on the remaining high-priority contaminants to fill identified data gaps. Stakeholders may be concerned that regulatory determinations for such contaminants should not necessarily wait until the end of the next regulatory determination cycle. In this regard, it is important to recognize that the Agency is not precluded from conducting research, monitoring, developing guidance or health advisories, and/or making a determination prior to the end of the next cycle. In addition, the Agency is not precluded from regulating a contaminant at any time when it is necessary to address an urgent threat to public health, including any contaminant not listed on the CCL.

Of the remaining CCL 2 contaminants, the Agency recognizes that the public may have a particular interest in perchlorate, metolachlor, methyl tertiary butyl ether (MTBE), and the microbial contaminants. Therefore, this report includes some additional information for these contaminants in the following sections.

Chapter 12: Perchlorate

A chapter from:

**Regulatory Determinations Support Document for Selected Contaminants
from the Second Drinking Water Contaminant Candidate List (CCL 2)**

EPA Report 815-D-06-007

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Abbreviations

AWS	American Water System
AWWARF	American Water Works Association Research Foundation
CA DHS	California Department of Health Services
CAS	Chemical Abstracts Service
CCL	Contaminant Candidate List
CDC	Centers for Disease Control
DW	Dry Weight
DWEL	Drinking Water Equivalent Level
FDA	Food and Drug Administration
FW	Fresh Weight
HRL	Health Reference Level
IC	Ion Chromatography
IC/MS	Ion Chromatography Mass Spectrometry
IC-MS/MS	Ion Chromatography Tandem Mass Spectrometry
IC-ESI-MS/MS	Ion Chromatography Electrospray Ionization Tandem Mass Spectrometry
IOC	Inorganic Compound
IRIS	Integrated Risk Information System
LC-MS/MS	Liquid Chromatography Tandem Mass Spectrometry
MA DEP	Massachusetts Department of Environmental Protection
MRL	Minimum Reporting Level or Minimum Reporting Limit
MS/MS	Tandem Mass Spectrometry
NAS	National Academies of Science
NCEH	National Center for Environmental Health
ND	Not Detected
NHANES	National Health and Nutrition Examination Survey
NIS	Sodium (Na ⁺) Iodide (I ⁻) Symporter
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NQ	Not Quantifiable
NRC	National Research Council
PWS	Public Water System
RDA	Recommended Daily Allowance
RfD	Reference Dose
RSC	Relative Source Contribution
TDS	Total Diet Study
TSH	Thyroid-Stimulating Hormone
UCMR 1	First Unregulated Contaminant Monitoring Regulation
USDA	United States Department of Agriculture
USDA-ARS	U.S. Department of Agriculture – Agricultural Research Service
WHO	World Health Organization

12 Perchlorate

12.1 Definition

Perchlorate is an inorganic contaminant (IOC) containing one chlorine atom bound to four oxygen atoms in a tetrahedral configuration. As such, perchlorate (ClO_4^-) is a group of anions that forms salts with most cations. Commonly used perchlorate salts include ammonium perchlorate and potassium perchlorate. Perchlorate is also used as sodium perchlorate, aluminum perchlorate, hydrazine perchlorate, hydrogen perchlorate, hydroxylammonium perchlorate, lithium perchlorate, magnesium perchlorate, nitronium perchlorate, and as perchloric acid. As an anion, there is no single Chemical Abstracts Service (CAS) registry for perchlorate, as each salt has its own properties. Registry numbers for the most common forms of perchlorate are presented in Exhibit 12-1.

12.1.1 Properties and Sources

Perchlorate (ClO_4^-) is an anion commonly associated with the solid salts of ammonium, magnesium, potassium, and sodium perchlorate. Although commonly known as a man-made chemical, perchlorate also may be derived from natural processes.

Chile possesses caliche ores rich in sodium nitrate (NaNO_3), which are also a natural source of perchlorate (Schilt, 1979 and Ericksen, 1983, as cited in USEPA, 2001). These Chilean nitrate salts (saltpeter) have been mined and refined to produce commercial fertilizers, which before 2001 accounted for about 0.14 percent of U.S. fertilizer application (USEPA, 2001). Perchlorate has also been found in other geologic materials. Orris *et al.* (2003) measured perchlorate at levels exceeding 1,000 parts per million (ppm or mg/kg) in several samples of natural minerals, including potash ore from New Mexico and Saskatchewan (Canada), playa crust from Bolivia, and hanksite from California.

Texas Tech University Water Resources Center conducted a large-scale sampling program to determine the source and distribution of perchlorate in northwest Texas groundwater (Jackson *et al.*, 2004; Rajagopalan *et al.*, 2006). Perchlorate was detected at concentrations greater than 0.5 $\mu\text{g/L}$ in 46 percent of public wells and 47 percent of private wells. Jackson *et al.* (2004) hypothesized that atmospheric production and/or surface oxidative weathering is the source of the perchlorate. In related research, Dasgupta *et al.* (2005) detected perchlorate in many rain and snow samples and demonstrated that perchlorate is formed by a variety of simulated atmospheric processes suggesting that natural, atmospherically-derived perchlorate exists in the environment. Barron *et al.* (2006) developed a method for the rapid determination of perchlorate in rainwater samples, with a detection limit between 70 and 80 ng/L. Of the ten rainwater samples collected in Ireland in 2005, perchlorate was detected in 4 samples at concentrations between 0.075 and 0.113 $\mu\text{g/L}$, and in 1 other sample at 2.8 $\mu\text{g/L}$. Kang *et al.* (2006) conducted seven-day experiments to determine if it was possible to produce perchlorate by exposing various chlorine intermediates to UV radiation in the form of high intensity UV lamps and/or ambient solar radiation. Perchlorate formation was demonstrated in aqueous salt solutions with initial concentrations of hypochlorite, chlorite, or chlorate between 100 and 10,000 mg/L.

After a limited investigation, the Massachusetts Department of Environmental Quality (MA DEP, 2005) found that perchlorate may be present in sodium hypochlorite solutions used in water and wastewater treatment plants, and that the level of occurrence depends upon storage conditions and the initial purity of the stock solution (MA DEP, 2005). According to MA DEP (2005), the Town of Tewksbury conducted a small study to evaluate the impact of storage conditions (temperature and light) on a new shipment of sodium hypochlorite stock solution. Tewksbury found that the perchlorate concentration in the new stock solution increased from 0.2 µg/L to levels ranging from 995 to 6,750 µg/L depending on the storage conditions. Accounting for the large dilution factor (e.g., 20,000 to 1 ratio) used in chlorination processes at drinking water treatment plants, MA DEP (2005) concluded that "absent additional efforts to minimize breakdown of hypochlorite solutions, it would appear that low levels of the perchlorate ion (0.2 to 0.4 µg/L) detected in a drinking water supply disinfected with sodium hypochlorite solutions could be attributable to the chlorination process."

It is not clear at this time what proportion of perchlorate found in public water supplies or entering the food chain comes from these various anthropogenic and natural sources. The significance of different sources probably varies regionally. A study by Dasgupta et al. (2006) analyzes the three principal sources of perchlorate and their relative contributions to the food chain. These are its use as an oxidizer including rocket propellants, Chilean nitrate used principally as fertilizer, and that produced by natural atmospheric processes.

Some physical and chemical properties of perchlorate and common perchlorate salts are listed in Exhibit 12-1.

Exhibit 12-1: Physical and Chemical Properties

Perchlorate and Its Common Salts					
	Perchlorate	Ammonium perchlorate	Potassium perchlorate	Magnesium perchlorate	Sodium perchlorate
CAS number	14797-73-0	7790-98-9	7778-74-7	10034-81-8	7601-89-0
Molecular Formula	ClO_4^-	NH_4ClO_4	KClO_4	$\text{Mg}(\text{ClO}_4)_2$	NaClO_4
Physical and Chemical Properties					
Boiling Point	-----	-----	400 °C ¹	-----	-----
Melting Point	-----	439 °C ²	525 °C ⁴	250 °C ⁴	480 °C ⁴
Molecular Weight	99.45 g/mol ¹	117.49 g/mol ²	138.55 g/mol ¹	223.20 g/mol ⁴	122.4 g/mol ¹
Water Solubility	-----	200 g/L @ 25°C ³	15 g/L @ 25°C ³	99 g/1000g @ 25°C ⁵	209 g/100 g @ 25 °C ⁶

¹ Budavari, 1996 (as cited in HSDB, 2004)

² HSDB, 2004

³ Ashford, 1994 (as cited in HSDB, 2004)

⁴ Lide, 2000 (as cited in HSDB, 2004)

⁵ Weast, 1979 (as cited in HSDB, 2004)

⁶ Gerhartz, 1985 (as cited in HSDB, 2004)

12.1.2 Environmental Fate and Behavior

Perchlorate salts are highly soluble in water, and because perchlorate sorbs poorly to mineral surfaces and organic material, perchlorate can be mobile in surface and subsurface aqueous environments (USEPA, 2002).

12.2 Health Effects

Perchlorate can interfere with the normal functioning of the thyroid gland by competitively inhibiting the transport of iodide into the thyroid. Iodide is an important component of two thyroid hormones, T4 and T3, and the transfer of iodide from the blood into the thyroid is an essential step in the synthesis of these two hormones. Iodide transport into the thyroid is mediated by a protein molecule known as the sodium (Na⁺) – iodide (I⁻) symporter (NIS). NIS molecules bind iodide with very high affinity, but they also bind other ions that have a similar shape and electric charge, such as perchlorate. The binding of these other ions to the NIS inhibits iodide transport into the thyroid, which can result in intrathyroidal iodide deficiency and consequently decreased synthesis of T4 and T3. There is compensation for iodide deficiency, however, such that the body maintains the serum concentrations of thyroid hormones within narrow limits through feedback control mechanisms. This feedback includes increased secretion of thyroid stimulating hormone (TSH) from the pituitary gland, which has among its effects the increased production of T4 and T3 (USEPA, 2005). Sustained changes in thyroid

hormone and TSH secretion can result in thyroid hypertrophy and hyperplasia (abnormal growth or enlargement of the thyroid) (USEPA, 2005).

In January 2005, the National Research Council (NRC) of the National Academies of Science (NAS) published “Health Implications of Perchlorate Ingestion,” a review of the current state of the science regarding potential adverse health effects of perchlorate exposure and mode-of-action for perchlorate toxicity (NRC, 2005). Based on recommendations of the NRC, EPA chose data from the Greer *et al.* (2002) human clinical study as the basis for deriving a reference dose (RfD) for perchlorate (USEPA, 2005). Greer *et al.* (2002) report the results of a well-controlled study that measured thyroid iodide uptake, hormone levels, and urinary iodide excretion in a group of 24 healthy adults administered perchlorate doses orally over a period of 14 days. Dose levels ranged from 0.007 to 0.5 mg/kg/day in the different experimental groups. No significant differences were seen in measured serum thyroid hormone levels (T3, T4, total and free) in any dose group. The statistical no-observed-effect level (NOEL) for perchlorate-induced inhibition of thyroid iodide uptake was 0.007 mg/kg/day. Although the NRC committee concluded that hypothyroidism is the first adverse effect in the continuum of effects of perchlorate exposure, NRC recommended that “the most health-protective and scientifically valid approach” was to base the perchlorate RfD on the inhibition of iodide uptake by the thyroid (NRC, 2005). NRC concluded that iodide uptake inhibition, although not adverse, is the key biochemical event in the continuum of possible effects of perchlorate exposure and would precede any adverse health effects of perchlorate exposure. The lowest dose (0.007 mg/kg/day) administered in the Greer *et al.* (2002) study was considered a NOEL (rather than a “no-observed-adverse-effect level” or NOAEL) because iodide uptake inhibition is not an adverse effect but a biochemical change (USEPA, 2005). A summary of the data considered and the NRC deliberations can be found in the NRC report (2005) and the EPA Integrated Risk Information System (IRIS) summary (USEPA, 2005).

The NRC recommended that EPA apply an intraspecies uncertainty factor of 10 to the NOEL to account for differences in sensitivity between the healthy adults in the Greer *et al.* (2002) study and the most sensitive population, fetuses of pregnant women who might have hypothyroidism or iodide deficiency. Because the fetus depends on an adequate supply of maternal thyroid hormone for its central nervous system development during the first trimester of pregnancy, iodide uptake inhibition from low-level perchlorate exposure has been identified as a concern in connection with increasing the risk of neurodevelopmental impairment in fetuses of high-risk mothers (NRC, 2005). The NRC (2005) viewed the uncertainty factor of 10 as conservative and health protective given that the point of departure is based on a non-adverse effect (iodide uptake inhibition) that precedes the adverse effect in a continuum of possible effects of perchlorate exposure. NRC concluded that no uncertainty factor was needed for the use of a less-than chronic study, for deficiencies in the database, or for interspecies variability. To protect the most sensitive human population from chronic perchlorate exposure, EPA derived an RfD of 0.0007 mg/kg/day with a ten-fold total uncertainty factor from the NOEL of 0.007 mg/kg/day (USEPA, 2005).

Blount *et al.* (2006b) recently published a study examining the relationship between urinary levels of perchlorate and serum levels of TSH and total T4 in 2,299 men and women (ages 12 years and older), who participated in the Centers for Disease Control’s (CDC’s) 2001-

2002 National Health and Nutrition Examination Survey (NHANES)¹. Blount *et al.* (2006b) evaluated perchlorate along with covariates known or likely to be associated with T4 or TSH levels to assess the relationship between perchlorate and these hormones, and the influence of other factors on this relationship. These covariates included sex, age, race/ethnicity, body mass index, serum albumin, serum cotinine (a marker of tobacco smoke exposure), estimated total caloric intake, pregnancy status, post-menopausal status, premenarche status, serum C-reactive protein, hours fasting before sample collection, urinary thiocyanate, urinary nitrate, and use of selected medications. The study found that perchlorate was a significant predictor of thyroid hormones in women, but not men.

After finding evidence of gender differences, the researchers focused on further analyzing the NHANES data for the 1,111 women participants. They divided these 1,111 women into two categories, higher-iodide and lower-iodide, using a cut point of 100 µg/L of urinary iodide based on the World Health Organization (WHO) definition of sufficient iodide intake². Hypothyroid women were excluded from the analysis. According to the study authors, about 36 percent of women living in the United States have urinary iodide levels less than 100 µg/L (Caldwell *et al.*, 2005). For women with urinary iodide levels less than 100 µg/L, the study found that urinary perchlorate is associated with a decrease in (a negative predictor for) T4 levels and an increase in (a positive predictor for) TSH levels. For women with urinary iodide levels greater than or equal to 100 µg/L, the researchers found that perchlorate is a significant positive predictor of TSH but not a predictor of T4. The study found that perchlorate was not a significant predictor of T4 or TSH in men. The researchers state that perchlorate could be a surrogate for another unrecognized determinant of thyroid function. Also, the study reports that while large doses of perchlorate are known to decrease thyroid function, this is the first time an association of decreased thyroid function has been observed at these low levels of perchlorate exposure. Of note is that the vast majority of the participants in this group had urinary levels of perchlorate corresponding to estimated dose levels that are below the RfD of 0.0007 mg/kg/day.

The clinical significance of the variations in T4/TSH levels, which were generally within normal limits, has not been determined. The researchers noted several limitations of the study (e.g., assumption that urinary perchlorate correlates with perchlorate levels in the stroma and tissue and preference for measurement of free T4 as opposed to total T4) and recommended that these findings be confirmed in at least one more large study focusing on women with low urine iodide levels. It is also not known whether the association between perchlorate and thyroid hormone levels is causal or mediated by some other correlate of both, although the relationship between urine perchlorate and total TSH and T4 levels persisted after statistical adjustments for some additional covariates known to predict thyroid hormone levels (e.g., total kilocalorie intake, estrogen use, and serum C-reactive protein levels). A planned follow-up study will include additional measures of thyroid health and function (e.g. TPO-antibodies, free T4). As EPA proceeds towards a regulatory determination for perchlorate, the Agency will continue to review any new findings/studies on perchlorate and their relationship to thyroid function as they become available.

1 While CDC researchers measured urinary perchlorate concentration for 2,820 NHANES participants, TSH and total T4 serum levels were only available for 2,299 of these participants.

2 WHO notes that the prevalence of goiter begins to increase in populations with a median iodide intake level below 100 µg/L (WHO, 1994).

12.3 Occurrence and Exposure

12.3.1 Use and Environmental Release

While perchlorate has a wide variety of industrial uses, it is primarily used in the form of ammonium perchlorate as an oxidizer in solid fuels used to power rockets, missiles, and fireworks. Approximately 90 percent of perchlorate is manufactured for this application (Wang *et al.*, 2002). Perchlorate can also be present as an ingredient or as an impurity in road flares, lubricating oils, matches, aluminum refining, rubber manufacturing, paint and enamel manufacturing, leather tanning, paper and pulp processing (as an ingredient in bleaching powder), and as a dye mordant.

Reports produced by USEPA (2002) and the American Water Works Association Research Foundation (AWWARF) (Wang *et al.*, 2002) summarize publicly available information on industrial production, consumption, and disposal of perchlorate.

As noted above, Chilean nitrate salts (saltpeter) have been mined and refined to produce commercial fertilizers. Before 2001, these accounted for about 0.14 percent of U.S. fertilizer application (USEPA, 2001). The USEPA (2001) conducted a broad survey of fertilizers and other raw materials and found that all products surveyed were devoid of perchlorate except for those known to contain or to be derived from mined Chilean saltpeter.

12.3.2 Ambient Water Occurrence

Ambient waters are lakes, rivers, and aquifers that serve as sources for drinking water. Limited national data on the occurrence of perchlorate in ambient surface and ground water have been compiled by EPA Region 9, are posted on the Internet by the Defense Environmental Network & Information Exchange (DENIX, 2004).

12.3.3 Drinking Water Occurrence

Nationally representative data on perchlorate occurrence in drinking water have been collected by large and small public water systems in accordance with EPA's first Unregulated Contaminant Monitoring Regulation (UCMR 1). For details on the UCMR 1, see Chapter 2 and USEPA (2006). Additional monitoring has been performed by other entities.

UCMR 1

EPA included perchlorate as an analyte in the 1999 Unregulated Contaminant Monitoring Regulation (UCMR 1) and collected drinking water occurrence data for perchlorate from 3,858 public water systems (PWSs) between 2001 and 2005. EPA analyzed the available UCMR 1 data on perchlorate at concentrations greater than or equal to 4 µg/L, the minimum reporting level (MRL) for EPA Method 314.0³. The Agency found that approximately 4.1 percent (or 160) of 3,858 PWSs that sampled and reported under UCMR 1 had at least 1 analytical detection of perchlorate (in at least 1 entry/sampling point) at levels greater than or equal to 4 µg/L. These

³ EPA Method 314.0 was the analytical method approved and used for UCMR 1 at the time of data collection.

160 systems are located in 26 states and 2 territories. Of these 160 PWSs, 8 are small systems (serving 10,000 or fewer people) and 152 are large systems (serving more than 10,000 people). Approximately 1.9 percent (or 637) of the 34,193 samples collected (by these 3,858 PWSs) had positive detections of perchlorate at levels greater than or equal to 4 µg/L. The maximum reported concentration of perchlorate was 420 µg/L, which was found in a surface water sample from a PWS in Puerto Rico. The average concentration of perchlorate for those samples with positive detections for perchlorate was 9.85 µg/L and the median concentration was 6.40 µg/L.

These 160 PWSs (with at least 1 analytical detection for perchlorate at levels greater than or equal to 4 µg/L) serve approximately 7.5 percent (or 16.8 million) of the 225 million people served by the 3,858 PWSs that sampled and reported results under UCMR 1. The 16.8 million population-served value represents the total number of people served by the 160 PWSs with at least one detect. Not all people served by these systems necessarily have perchlorate in their drinking water. Some of these 160 public water systems have multiple entry points to the distribution system and not all of the entry points sampled had positive detections for perchlorate in the UCMR 1 survey. An alternative approach to the system-level assessment of populations served is to use an assessment at the entry (sampling) point level⁴. EPA does not have population-served values for each entry point at the system level. However, an assessment can be performed by assuming that each entry (or sampling) point at a public water system serves an equal proportion of the total population-served by the system. In other words, for the alternative assessment, the population served by each system is assumed to be equally distributed across all entry (or sampling) points at each system. For example, if a system serves a million people and has 5 entry points, it is assumed that each entry point serves 200,000 people. Using this approach and counting only the population served for the entry points with positive detections (concentrations greater than or equal to 4µg/L), the total population served by these entry points with perchlorate detections is approximately 5 million. Section 12.4 provides the number of systems and population-served estimates for other thresholds of interest.

California Monitoring

The California Department of Health Services (CA DHS) began monitoring for perchlorate in 1997. In 1999, CA DHS began requiring monitoring for perchlorate for drinking water sources that were identified as vulnerable to perchlorate contamination under California's own State monitoring program (i.e., Unregulated Chemicals for which Monitoring is Required). About 60 percent (or 7,100) of all drinking water sources in California (about 12,000) were monitored for perchlorate under the State monitoring program. Between June 2001 and June 2006, CA DHS (2006) reports that 284 (about 4%) of the approximately 7,100 water sources that monitored had at least 2 or more positive detections for perchlorate at concentrations greater than or equal to 4 µg/L (the reporting limit). These 284 sources supply water for 77 drinking water

⁴ EPA acknowledges that uncertainties exist in the population-served estimates for this alternative assessment since the population for a system is assumed to be equally distributed across the entry points for that system. Because the actual population-served by an entry point is not known, this alternative approach has an equal chance of underestimating or overestimating the actual population-served by entry points with positive detections for perchlorate. In addition, this approach could underestimate the population served that is potentially exposed to perchlorate and overestimate the level of exposure because it can not incorporate the effects of mixing of water between different entry points within the distribution system. This is because the approach cannot account for the dilution that may occur when water that has no detections of perchlorate is mixed within the distribution system with water that has positive detections for perchlorate.

systems (CA DHS, 2006) and represent active and standby sources (and exclude inactive, destroyed, and abandoned sources, and monitoring and agricultural wells) (CA DHS, 2006).

Massachusetts Monitoring

In 2005, the State of Massachusetts's Department of Environment Protection (MA DEP) reported monitoring results for 85 percent (379 of 450) of its community water systems and 86 percent (212 of 250) of its non-transient, non-community water systems. MA DEP found that 9 (1.5%) of the 591 public water systems detected perchlorate at levels greater than or equal to 1 µg/L (the reporting limit used for a modified version of EPA Method 314.0). MA DEP found that the occurrence of perchlorate for these water systems could be traced to the use of blasting agents, military munitions, fireworks, and, to a lesser degree, sodium hypochlorite disinfectant (MA DEP, 2005).

Texas High Plains Monitoring

As noted above, Texas Tech University Water Resources Center conducted a large-scale sampling program to determine the source and distribution of perchlorate in northwest Texas groundwater (Jackson *et al.*, 2004; Rajagopalan *et al.*, 2006). Perchlorate was detected at concentrations greater than 0.5 µg/L in 46 percent of public wells and 47 percent of private wells. Jackson *et al.* (2004) hypothesized that atmospheric production and/or surface oxidative weathering is the source of the perchlorate. Additional results from the same research team are presented in Jackson *et al.* (2005).

Additional Drinking Water Studies

At least two other states have published investigations of perchlorate occurrence in drinking water: Arizona (ADEQ *et al.*, 2004) and New Jersey (NJDWQI, 2005). In addition, AWWARF sponsored a nationwide survey of perchlorate occurrence (Wang *et al.*, 2002). And the American Water System (AWS), which manages dozens of PWSs nationwide, published its own internal survey of perchlorate occurrence in source water (Gullick *et al.*, 2001).

12.3.4 Studies on Perchlorate Occurrence in Foods, Beverages, and Dietary Supplements

The Food and Drug Administration (FDA), the United States Department of Agriculture (USDA), and researchers from academia and industry have studied perchlorate in foods. Some of these studies are described briefly in this section, and also summarized in Exhibit 12-2. EPA has concluded that the sampling results described in this section and Exhibit 12-2 are too limited to characterize food-borne exposure to perchlorate on a national scale. The sampling data are limited in the types of foods sampled, sample sizes, geographic coverage, and/or analytical method adequacy and many were targeted to foods or areas known or likely to have elevated levels of perchlorate. Section 12.5 of this document describes the limitations of the food sampling data and also describes plans for including perchlorate as part of the FDA's Total Diet Study.

Exhibit 12-2: Summary Data on Perchlorate Occurrence in Food Items

Food Item	Data Reference	Units	N	MRL	Range of Detection s	Reported Mean^s	Rate of Detection (percent)	Sample Locations
Iceberg Lettuce	FDA (2004) ^a	µg/kg FW	38	1	<MRL – 71.6	7.76	79% ^b	AZ, CA, FL, NJ
	Sanchez <i>et al.</i> (2005a) ^c	µg/kg FW	44	~20	<MRL - 26	NA	86%	AZ, CA
	Sanchez <i>et al.</i> (2005a) ^f	µg/kg FW	24	25-30	ND - 24	10	NA	AZ, CA
	Sanchez <i>et al.</i> (2005b) ^f	µg/kg FW	63	20-40	ND - 31	7.4	NA	See note ^m
Romaine Lettuce	FDA (2004) ^a	µg/kg FW	40	1	<MRL - 129	11.9	95% ^b	AZ, CA, FL, NJ, TX
	Sanchez (2004) ^e	µg/kg FW	7	20 - 50	<MRL - 81	NA	100%	AZ, CA
	Sanchez <i>et al.</i> (2005a) ^d	µg/kg FW	24	25-30	ND - 20	13	NA	AZ, CA
	Sanchez <i>et al.</i> (2005b) ^e	µg/kg FW	84	20-40	ND - 100	17.1	NA	See note ^m
Green Leaf Lettuce	FDA (2004) ^a	µg/kg FW	25	1	1.00 – 27.4	10.7	100%	AZ, CA, NJ, TX
	Sanchez (2004) ^e	µg/kg FW	3	20 - 50	46-64	NA	100%	AZ, CA
	Sanchez <i>et al.</i> (2005a) ^e	µg/kg FW	24	25-30	ND - 102	33	NA	AZ, CA
	Sanchez <i>et al.</i> (2005b) ^e	µg/kg FW	69	20-40	ND - 195	16.5	NA	See note ^m
Red Leaf Lettuce	FDA (2004) ^a	µg/kg FW	25	1	<MRL – 52.0	11.6	92% ^b	AZ, CA, TX
	Sanchez <i>et al.</i> (2005a) ^e	µg/kg FW	24	25-30	ND - 81	27	NA	AZ, CA
	Sanchez <i>et al.</i> (2005b) ^e	µg/kg FW	67	20-40	ND - 104	14.5	NA	See note ^m
Butterhead Lettuce	Sanchez <i>et al.</i> (2005a) ^e	µg/kg FW	24	25-30	ND - 104	29	NA	AZ, CA
	Sanchez <i>et al.</i> (2005b) ^e	µg/kg FW	45	20-40	ND - 98	17.2	NA	See note ^m
Arugula	Sanchez <i>et al.</i> (2005b) ^e	µg/kg FW	9	20-40	ND - 195	55.8	NA	See note ^m
Spinach	Sanchez <i>et al.</i> (2005b) ^e	µg/kg FW	10	20-40	ND - 628	85.1	NA	See note ^m

Food Item	Data Reference	Units	N	MRL	Range of Detection s	Reported Mean ^s	Rate of Detection (percent)	Sample Locations
Bottled Water	FDA (2004)	µg/L	51	0.5	<MRL – 0.56	NA	4% ^b	CA, CO, GA, MD, MN, MO, NC, NE, PA, SC, TX, WI
Dairy Milk	FDA (2004)	µg/L	104	3	<MRL – 11.3	5.76	97% ^b	AZ, CA, GA, KS, LA, MD, MO, NJ, NC, PA, SC, TX, VA, WA
	Kirk <i>et al.</i> (2005)	µg/L	47	~1 ^g	ND – 11.0	2.0	98%	AK, AZ, CA, FL, HI, KS, ME, NH, NM, NY, PA
	Kirk <i>et al.</i> (2003)	µg/L	7	0.5 ^g	1.7 – 6.4	NA	100%	TX
Melon	Sanchez (2004) ^h	µg/kg FW	25	20 - 50	ND - <MRL	NA	48%	AZ, CA
	Jackson <i>et al.</i> (2005) ⁱ	µg/kg FW	1	NA	1600	NA	100%	KS
Cucumber	Jackson <i>et al.</i> (2005) ⁿ	µg/kg FW	2	NA	40 - 770	NA	100%	TX, KS
Tomato	Sanchez (2004)	µg/kg FW	8	20 - 50	ND - <MRL	NA	37%	AZ, CA
	Jackson <i>et al.</i> (2005)	µg/kg FW	2	NA	42 - 220	NA	100%	KS
Pepper	Sanchez (2004)	µg/kg FW	10	20 - 50	ND - <MRL	NA	30%	AZ, CA
Carrot	Sanchez (2004)	µg/kg FW	10	20 - 50	ND	NA	0%	CA
Onion	Sanchez (2004)	µg/kg FW	10	20 - 50	ND	NA	0%	CA
Sweet Corn	Sanchez (2004)	µg/kg FW	18	20 - 50	ND	NA	0%	AZ, CA

Food Item	Data Reference	Units	N	MRL	Range of Detection s	Reported Mean ^s	Rate of Detection (percent)	Sample Locations
Squash	Sanchez (2004)	µg/kg FW	10	20 - 50	ND	NA	0%	AZ, CA
Wheat	Sanchez (2004) ^j	µg/kg FW	NA	20 - 50	ND	NA	0%	AZ
	Jackson <i>et al.</i> (2005) ^k	µg/kg FW	12	NA	710 – 4400 ^l	NA	100%	TX
Alfalfa	Sanchez (2004) ^o	µg/kg FW	10	20 - 50	109 - 668	NA	100%	AZ, CA
	Jackson <i>et al.</i> (2005) ^p	µg/kg FW	3	NA	NA	2900	100%	TX
Soy Milk	Kirk <i>et al.</i> (2005)	µg/L	1	~1 ^g	0.7	NA	100%	TX
Lemon	Sanchez <i>et al.</i> (2006)	µg/kg FW	33	~2.5	ND – 14.8	2.3	NA	AZ, CA
Grapefruit	Sanchez <i>et al.</i> (2006)	µg/kg FW	15	~2.5	ND – 16.2	3.3	NA	AZ, CA
Orange	Sanchez <i>et al.</i> (2006)	µg/kg FW	28	~2.5	ND – 37.6	7.4	NA	AZ, CA
Seaweed	Martinelango <i>et al.</i> (2006a) ^q	µg/kg DW	13	NA	29 - 878	NA	100%	Atlantic Ocean (ME)
Beer	Aribi <i>et al.</i> (2006)	µg/L	144	NA	0.005 – 21.096	NA	100%	47 countries (including USA)
	Aribi <i>et al.</i> (2006)	µg/L	8	NA	0.364 – 2.014	0.662 ^r	100%	USA
Wine	Aribi <i>et al.</i> (2006)	µg/L	77	NA	0.029 – 50.25	NA	100%	22 countries (including USA)
	Aribi <i>et al.</i> (2006)	µg/L	12	NA	0.197 – 4.593	2.09 ^r	100%	USA

Notes:

N = number of samples; MRL = minimum reporting limit; ND = not detected; FW = fresh weight; DW = dry weight; NA = not available from (or not appropriate for) the cited study.

^a Outermost leaves of each lettuce head were removed prior to sample analysis.

^b Rate of detection is based on number of samples for which perchlorate was quantifiable (not just detectable).

^c Samples are of “edible head” (trimmed of frame and wrapper leaves).

^d Samples are “bulk” (partial removal of stem core and partial severing of upper and outer leaf blade margins).

^e Samples preparation included minimal trimming.

^f Samples have had multiple layers of their outer wrapper leaves removed.

^g Value reported as the “limit of detection.”

^h Samples include cantaloupe, casaba, honey dew, galia, and watermelon.

ⁱ Sample of cantaloupe from a home garden in Morris County, KS.

^j Durum wheat.

^k Whole wheat head, including seed (endosperm), bran, germ, and chaff.

^l Represents the range of average values (3 samples, each) of 4 commercial growing fields in Gaines County, TX. In partitioned samples, perchlorate in the whole grain (not including the chaff) measured 1300 µg/kg FW in 1 sample and was not detected in 2 samples of wheat endosperm.

^m Study was restricted to foods outside the lower Colorado River region. Sample locations were not presented for each food item, however, the complete list of regions sampled is CA, CO, MI, NJ, NM, NY, OH, and Quebec.

ⁿ Samples were collected from home gardens in Gaines County, TX, and Morris County, KS.

^o Six of the ten alfalfa samples were sent to FDA for confirmatory analysis by ion chromatography-tandem mass spectrometry (IC-MS/MS). The FDA results ranged from 121 to 382 µg/kg FW.

^p Samples were collected from a single commercial growing field in Gaines County, TX.

^q Samples of 11 different commercially available species were collected.

^r Value provided is the median (not the mean).

^s When comparing means from the studies it is important to note that the different studies likely treated non-detects differently. Some studies treated non-detects as one-half the MRL and others treated non-detects as zero.

FDA Targeted Sampling

The FDA released data on perchlorate in milk, lettuce, and bottled water in November 2004. To analyze food samples, FDA used ion chromatography (IC)-tandem mass spectrometry (MS/MS), referred to as IC-MS/MS. The quantitation limits for perchlorate in these analyses were 0.5 µg/L for bottled water, 1 µg/kg by fresh weight (FW) for lettuce, and 3 µg/L for dairy milk. The mean concentration of perchlorate in 128 lettuce samples collected in 5 states (AZ, CA, FL, NJ, TX) was 10.3 µg/kg FW (FDA, 2004), and ranged from not quantifiable (NQ) to 129 µg/kg FW. The mean concentrations of perchlorate in several varieties of lettuce are reported in Exhibit 12-2. The mean concentration of perchlorate in 104 dairy milk samples collected in 14 states (AZ, CA, GA, KS, LA, MD, MO, NJ, NC, PA, SC, TX, VA, WA) was 5.76 µg/L (FDA, 2004), with a range from NQ to 11.3 µg/L. FDA (2004) detected perchlorate in 2 of the 51 bottled water samples representing 34 distinct sources collected in 12 states (CA, CO, GA, MD, MN, MO, NC, NE, PA, SC, TX, WI) at levels of 0.56 µg/L and 0.45 µg/L.

Other Published Studies

Sanchez (2004) and Sanchez *et al.* (2005a) report the results of an analysis of agricultural products sampled from the lower Colorado River region of Arizona and California, the Imperial Valley of California, and the Coachella Valley of California, where irrigation water is known or suspected to contain perchlorate. The studies were partially supported by the U.S. Department of Agriculture – Agricultural Research Service (USDA-ARS). Samples of iceberg, romaine, and leaf lettuce, carrots, onions, sweet corn, squash, melons, tomatoes, peppers, broccoli, cauliflower, cabbage, durum wheat, and alfalfa were analyzed for perchlorate using IC as the primary analytical method. For these analyses, the fresh-weight method reporting limit was not identified in most cases, but was reported to range from 20 to 50 µg/kg FW, depending on the moisture content of the samples (Sanchez, 2004). Sanchez *et al.* (2005a) report that the method reporting level for iceberg lettuce was approximately 20 µg/kg FW and for other types of lettuce was 25-30 µg/kg FW. Perchlorate in the irrigation water ranged from 1.5 to 8.0 µg/L over the period of the survey (Sanchez *et al.*, 2005a).

Sanchez *et al.* (2005a) analyzed 44 samples of iceberg lettuce heads that had been trimmed of frame and wrapper leaves, which are usually removed before the lettuce is consumed. Perchlorate was quantified in 5 of the samples (ranging from 23 to 26 µg/kg FW)⁵, perchlorate was not detectable in 6 samples, and the results of the remaining samples were less than the method reporting limit, which the authors defined as “a detectable peak among duplicates and/or replicates but below a level that can be quantitated.” Perchlorate concentrations in 10 samples of romaine and green leaf lettuce ranged from less than the method reporting limit to 81 µg/kg FW (Sanchez, 2004).

As shown in Exhibit 12-2, Sanchez (2004) also detected perchlorate in samples of melons, tomatoes, and peppers, but at levels below the method reporting limit. Perchlorate was not detected in carrots, onions, sweet corn, squash, and durum wheat. Concentrations of

⁵ Sanchez (2004) presents somewhat different results. Specifically, of the 44 samples of “edible head” lettuce, perchlorate was quantified in one of the samples (26 µg/kg), perchlorate was not detectable in 6 samples, and the remaining sampling results were qualified as <MRL, which the author defined as “represents a seemingly detectable peak but below a level that can be quantitated.”

perchlorate in 10 samples of alfalfa ranged from 109 to 668 $\mu\text{g/kg}$ FW. Six of the 10 alfalfa samples were sent to FDA for confirmatory analysis by IC-MS/MS. The FDA results were generally lower than those of the corresponding samples by Sanchez (2004), ranging from 121 to 382 $\mu\text{g/kg}$ FW.

Sanchez *et al.* (2006) conducted studies to evaluate the uptake and distribution of perchlorate in citrus trees and the occurrence of perchlorate in lemons, grapefruit, and oranges grown in southern California and southwestern Arizona. Five whole lemon trees irrigated with Colorado River water were harvested for destructive sampling. Sanchez *et al.* (2006) estimate that the irrigation water had an average perchlorate concentration of 6 $\mu\text{g/L}$. Most of the sample analysis was conducted using IC-MS/MS, having an MRL of approximately 25 $\mu\text{g/kg}$ by dry weight (DW). In samples of tree trunks, roots, and branches, perchlorate was close to or below the MRL. Perchlorate was much higher in the leaves than the fruit (peel and pulp), with mean concentrations of 1,835 and 128 $\mu\text{g/kg}$ DW, respectively.

Citrus samples were collected during 2004-2005 from the lower Colorado River Valley, the University of Arizona Research Farm, the Coachella Valley, and Los Angeles County. All analyses of fruit pulp were conducted using IC-MS/MS with an approximate MRL of 2.5 $\mu\text{g/kg}$ FW. For the 86 citrus samples collected, the perchlorate concentration in the fruit pulp ranged from below detection to 37.6 $\mu\text{g/kg}$ FW. Mean concentrations in lemons (33 samples), grapefruit (15 samples), and oranges (28 samples) were 2.3, 3.3, and 7.4 $\mu\text{g/kg}$ FW, respectively.

Sanchez *et al.* (2005b) surveyed perchlorate occurrence in lettuce and other leafy vegetables produced outside the lower Colorado River region. Samples were analyzed by IC, with a minimum reporting level of approximately 20 to 40 $\mu\text{g/kg}$ FW, depending on the leafy vegetable type. Results of some of the more heavily sampled food items are presented in Exhibit 12-2.

While not shown in Exhibit 12-2, Sanchez *et al.* (2005b) performed additional analysis by partitioning the leafy vegetable samples by type of culture. Perchlorate was detected in 70 of 268 samples of conventionally-grown leafy vegetables and 72 of 170 samples of organically-grown leafy vegetables. The range of perchlorate concentrations was not detected (ND) to 104 $\mu\text{g/kg}$ FW in conventional leafy vegetables and ND to 628 $\mu\text{g/kg}$ FW in organic leafy vegetables. Sanchez *et al.* (2005b) analyzed the results using regression analysis and estimated that the median perchlorate concentration in organically-grown samples was 2.2 times higher than in conventionally-grown samples. The regression analysis also suggested that variation among sampling locations was greater than variation among lettuce types.

Researchers at Texas Tech University analyzed samples of dairy and soy milk using IC and/or IC/MS analytical methods with detection limits of 1 $\mu\text{g/L}$ or better (Kirk *et al.*, 2005). In a study of perchlorate in dairy milk, Kirk *et al.* (2005) found mean perchlorate levels of 2.0 $\mu\text{g/L}$ in 47 retail dairy milk samples from 11 states (AK, AZ, CA, FL, HI, KS, ME, NH, NM, NY, PA), with a range from not ND to 11.0 $\mu\text{g/L}$. A single sample of soy milk was analyzed and reported to contain 0.7 $\mu\text{g/L}$ perchlorate (Kirk *et al.*, 2005). An earlier study by Kirk *et al.* (2003) found perchlorate ranging from 1.7 $\mu\text{g/L}$ to 6.4 $\mu\text{g/L}$ in 7 dairy milk samples purchased in a city in Texas.

Jackson *et al.* (2005) conducted limited sampling of edible and forage vegetation in 1 Texas county and in 1 Kansas home garden. In Texas, wheat and alfalfa were sampled from commercial fields irrigated with groundwater containing perchlorate from an unknown source, and a cucumber was sampled from an irrigated home garden. In Kansas, cantaloupe, cucumber, and tomatoes were sampled from an irrigated home garden near a slurry explosives site. Researchers used IC for sample analysis but did not report fresh-weight detection limits. Perchlorate was detected in all 12 samples of winter wheat heads (whole, including the chaff) at a mean concentration of 2,000 µg/kg FW but perchlorate was not detected in wheat endosperm (2 samples)⁶. The mean perchlorate concentration in 3 samples of alfalfa was 2,900 µg/kg FW. A cucumber sample from a Texas home garden contained 40 µg/kg FW perchlorate; a sample of irrigation water from this garden contained 20.7 µg/L perchlorate. In the Kansas home garden, the cucumber sample contained 770 µg/kg FW perchlorate, the cantaloupe sample contained 1,600 µg/kg FW perchlorate, and 2 samples of tomato contained 42 and 220 µg/kg FW perchlorate. The reported concentration of perchlorate in irrigation water for the Kansas home garden was 81 µg/L. EPA notes that the perchlorate levels in irrigation water samples associated with these two home gardens were significantly higher than in the vast majority of surface and ground water samples in the US.

Aribi *et al.* (2006) developed an analytical method for perchlorate that uses ion chromatography with suppressed conductivity and electrospray ionization tandem mass spectrometry (IC-ESI-MS/MS). The method was used to measure perchlorate in samples of various food products, including fresh/canned fruits and vegetables, wine, beer, and other beverages. Most samples were purchased in grocery and liquor stores in greater Toronto, Canada, between January 2005 and February 2006. Produce samples originated from many different parts of the world and all samples contained measurable amounts of perchlorate. However, the survey was limited to only a few samples of each food. Products from California, Chile, Costa Rica, Guatemala, and Mexico had the highest levels of perchlorate. Products from Canada and China had the lowest levels of perchlorate. The highest detection was in cantaloupe from Guatemala (463.50 µg/kg FW). Analysis of raw asparagus (39.900 µg/kg FW) and cooked asparagus (24.345 µg/kg FW) demonstrated that perchlorate can remain in food processed at a high temperature. Perchlorate concentrations in 8 samples of produce from the U.S. ranged from 0.094 µg/kg FW (for blueberries) to 19.29 µg/kg FW (for green grapes).

Aribi *et al.* (2006) analyzed 77 samples of wine and 144 samples of beer from many parts of the world. All samples contained measurable amounts of perchlorate. The wine sample with the single highest concentration of perchlorate, 50.250 µg/L, was from Portugal. Overall, wine samples from Chile contained the highest concentrations of perchlorate, ranging from 5.358 to 38.88 µg/L in 8 samples. Twelve samples of wine from the U.S. contained perchlorate concentrations ranging from 0.197 to 4.593 µg/L. Results from analysis of beer samples varied substantially among countries, with an overall range from 0.005 µg/L (Ireland) to 21.096 µg/L (France). Concentrations of perchlorate in 8 beer samples from the U.S. ranged from 0.364 to 2.014 µg/L.

6 A wheat kernel (seed) has three major parts - the bran, the germ, and the endosperm. The majority of the wheat kernel is the endosperm, which is the portion of the kernel that is retained in refined (white) wheat flours. Whole wheat flours contain endosperm, wheat bran, and wheat germ in approximately the same proportions as in the wheat kernel. Wheat flours do not contain the chaff (husk).

Snyder *et al.* (2006) measured perchlorate in dietary supplements and flavor enhancing ingredients collected from various vendors in Las Vegas, NV, and Seattle, WA. Analyses were performed using liquid chromatography tandem mass spectrometry (LC-MS/MS) with a limit of detection between 2 and 5 µg/kg. Perchlorate was detected in 20 of 31 analyzed supplements, with detectable concentrations ranging from 10 to 2,420 µg/kg. Based on manufacturers' recommended intake of the supplements, the resulting daily oral doses of perchlorate would range from 0.03 to 18 µg/day. Twelve of the supplements tested were prenatal or children's vitamins. The highest level of perchlorate (2,420 µg/kg or 0.018 mg/day at the recommended daily dose) was found in a prenatal vitamin; in the remaining prenatal and children's vitamins perchlorate did not exceed 28 µg/kg. The study noted that "vitamin and mineral supplements are typically formulated to include the Recommended Daily Allowance (RDA) of iodine, a factor that would provide protection against any possible impacts of microgram levels of perchlorate found in these supplements." Perchlorate was also detected at 740 µg/kg in a sample of kelp granules (a flavor enhancer), which equates to 2.2 µg perchlorate per serving.

Martinelango *et al.* (2006a) measured perchlorate in seaweed, which is often used as a source of iodide in food and nutritional supplements. Martinelango *et al.* (2006a) collected samples of 11 different species of seaweed growing off the coast of northeastern Maine. Perchlorate was detected in all species, with concentrations ranging from 29 to 878 µg/kg DW. The iodide content in the samples was much higher, ranging from 16 to 3,134 mg/kg DW. Martinelango *et al.* (2006a) found that samples of *Laminaria* species concentrated iodide more selectively than perchlorate. *Laminaria* is a genus of large brown seaweeds that are commonly used in kelp tablets. Martinelango *et al.* (2006a) also analyzed 4 seaweed samples that had been washed with deionized water and found that a single wash removed 38 to 73 percent of the perchlorate and 34 to 44 percent of the iodide.

12.3.5 Occurrence Studies on Perchlorate in Human Urine, Breast Milk, and Amniotic Fluid

Recently researchers have used the results of the analysis of urine samples to estimate human exposure to perchlorate. Ingested perchlorate is not metabolized by humans and is excreted largely in the urine (Merrill *et al.*, 2005). The CDC's National Center for Environmental Health (NCEH) developed a sensitive and selective analytical method to analyze perchlorate in human urine (Valentín-Blasini *et al.*, 2005). The method uses ion chromatography coupled with electrospray ionization tandem mass spectrometry (IC-ESI-MS/MS) and achieves an MRL of 0.025 µg/L in human urine. The authors report that the method is robust enough to process first-morning-void urine samples, which are samples of the first voiding of urine upon waking.

Valentín-Blasini *et al.* (2005) analyzed urine samples from 61 healthy adult donors who lived in the area of Atlanta, Georgia. The urine samples were provided anonymously, without associated donor information. Perchlorate was detected in all of the urine samples, with concentrations ranging from 0.66 to 21 µg/L. The authors cited dietary exposure as a potential source of perchlorate because perchlorate was found only at low levels (0.1 – 0.2 µg/L) in area tap water samples (Valentín-Blasini *et al.*, 2005).

Valentín-Blasini *et al.* (2005) also analyzed the urine samples for creatinine, which is a metabolic breakdown product in muscles that is eliminated from the body in urine at a predictable rate. When adjusted for urinary creatinine content, the reported range of perchlorate in the samples is 1.0 to 35 μg of perchlorate per gram of creatinine. The median perchlorate concentration was 3.2 $\mu\text{g/L}$ (7.8 $\mu\text{g/g}$ creatinine). The researchers stated that only 1 sample from the Atlanta population contained perchlorate at a level slightly in excess of the amount expected to be excreted by an individual exposed to perchlorate at the reference dose of 0.0007 mg/kg/day (Valentín-Blasini *et al.*, 2005). Specifically, assuming that perchlorate is excreted uniformly in urine throughout the day, a urinary excretion level of 34 μg perchlorate per gram creatinine would be associated with a daily perchlorate intake of 0.0007 mg/kg/day, for a 70 kg male that excretes creatinine at a typical rate of 1.44 grams per day (g/day). These assumptions are imprecise for individual exposure assessment but allow for spot urine perchlorate excretion to be related to the reference dose for toxicological perspective. Estimating perchlorate exposure from a single spot urine sample (as opposed to a sample collected continuously over a period of time) is imprecise due to the episodic nature of perchlorate exposure and the short half-life of perchlorate in the human body. The precision of estimated individual perchlorate exposure can be improved by more precise estimation of 24-hour creatinine excretion based on sex, height, weight, and age as described by Mage *et al.* (2004). In addition, imprecision stemming from the episodic nature of perchlorate exposure can be reduced with increased sampling.

The analytical method developed by Valentín-Blasini *et al.* (2005) was further used by Blount *et al.* (2006a) to evaluate urine samples from 27 volunteers with differing dietary habits. Blount *et al.* (2006a) collected first-morning-void urine specimens from volunteers living in the Atlanta area. The study volunteers self-assessed their consumption of milk, dairy products, and green/leafy vegetables within the 16 hours before the sample was collected. The samples were grouped into 2 categories (“one or fewer servings” and “three or more servings”) based on total consumption of these selected foods. Total daily perchlorate exposure was calculated using a bodyweight of 70 kg and a creatinine excretion rate of 1.44 g/day, assuming that each first-morning void urine sample was representative of that individual’s daily perchlorate exposure. Each volunteer also collected a drinking water sample from home and work. Blount *et al.* (2006a) analyzed drinking water samples with the same method used for urine analysis and estimated exposure from drinking water based on a body weight of 70 kg and daily consumption of 2 liters of water per day. The mean creatinine-adjusted urinary perchlorate level was 1.8 times higher for individuals who identified themselves as consuming three or more servings of milk, dairy products, and/or green/leafy vegetables (6.13 versus 3.45 $\mu\text{g/g}$ creatinine). There were no significant differences in the perchlorate levels in the drinking water samples of the 2 diet groups, which ranged from <0.05 to 0.25 $\mu\text{g/L}$ with a median of 0.10 $\mu\text{g/L}$. Using a median drinking water level of 0.10 $\mu\text{g/L}$, Blount *et al.* (2006a) estimated that the perchlorate dose from drinking water was 0.003 $\mu\text{g/kg/day}$. Compared to this drinking water estimate, the total perchlorate dose estimate based on mean urinary perchlorate excretion was 24 times higher (0.071 $\mu\text{g/kg/day}$) and 42 times higher (0.126 $\mu\text{g/kg/day}$) for the low-consumption and high-consumption diet groups, respectively. The overall range of perchlorate found in urine was 0.94 to 17 $\mu\text{g/g}$ creatinine with a median of 4.2 $\mu\text{g/g}$ creatinine.

In the largest study of its kind, Blount *et al.* (2006c) measured perchlorate in urine samples collected from a nationally representative sample of 2,820 U.S. residents, ages 6 years and older, as part of the 2001-2002 NHANES. Blount *et al.* (2006c) detected perchlorate at

concentrations greater than 0.05 µg/L in all 2,820 urine samples tested, with a median concentration of 3.6 µg/L (3.38 µg/g creatinine) and a 95th percentile of 14 µg/L (12.7 µg/g creatinine). Only 0.7 % of the study participants had an estimated perchlorate dose in excess of 0.0007 mg/kg/day. Women of reproductive age (15-44 years) had a median urinary perchlorate concentration of 2.9 µg/L (2.97 µg/g creatinine) and a 95th percentile of 13 µg/L (12.1 µg/g creatinine). The demographic with the highest concentration of urinary perchlorate was children (6-11 years), who had a median urinary perchlorate concentration of 5.2 µg/L (5.79 µg/g creatinine). Blount *et al.* (2006c) estimated a total daily perchlorate dose for each adult and found a median dose of 0.066 µg/kg/day (about one tenth of the RfD) and a 95th percentile of 0.234 µg/kg/day (about one third of the RfD). Eleven adults (0.7%) had estimated perchlorate exposure in excess of the RfD (0.7 µg/kg/day). The highest estimated exposure was 3.78 µg/kg/day. Because of daily variability in diet and perchlorate exposure, and the short residence time of perchlorate in the body, these single sample measurements may overestimate long-term average exposure for individuals at the upper end of the distribution and may underestimate the long term average exposure for individuals at the lower end of the distribution. Daily perchlorate dose is not presented for children and adolescents due to the limited validation of formulas for these age groups (Blount *et al.*, 2006c).

Valentín-Blasini *et al.* (2005) and Téllez *et al.* (2005) analyzed urine samples of pregnant women in 3 cities in Chile and found higher median levels of urinary perchlorate in cities with higher concentrations of perchlorate in tap water. Based on an assessment of drinking water intake, the researchers determined that, in all 3 cities, there was an additional source of perchlorate for the study participants that may be explained by dietary (food) intake (Téllez *et al.*, 2005). This gap between estimated perchlorate exposure and perchlorate intake from tap water consumption ranged from 21.7 µg/day to 33.8 µg/day in the three Chilean cities (Téllez *et al.*, 2005).

Martinelango *et al.* (2006b) developed a method to measure perchlorate in human urine with a limit of detection of 0.080 µg/L, and reported analytical results of 9 spot urine samples from male and female volunteers. Perchlorate was present in all samples analyzed, at concentrations ranging from 2.2 to 14.9 µg/L, with a median value of 8.1 µg/L.

Other studies have investigated perchlorate in human breast milk. Kirk *et al.* (2005) analyzed 36 breast milk samples from 18 states (CA, CT, FL, GA, HI, MD, ME, MI, MO, NC, NE, NJ, NM, NY, TX, VA, WA, WV) and found perchlorate concentrations in all samples ranging from 1.4 to 92.2 µg/L in all samples, with a mean concentration of 10.5 µg/L. Téllez *et al.* (2005) report maternal parameters for participants from the study in Chile. Breast milk samples indicated that a significant amount of perchlorate leaves the body of the nursing mother through breast milk, in addition to urine. However, the breast milk perchlorate levels were highly variable and no significant correlations could be established between breast milk perchlorate and either urine perchlorate or breast milk iodide concentrations for the individuals evaluated in these Chilean cities (Téllez *et al.*, 2005). Kirk *et al.* (2006) evaluated variations of iodide, thiocyanate and perchlorate in human milk samples. These authors suggest that if the overall intake of iodide is sufficient, it is unlikely that milk with an occasional low iodide or high perchlorate content would pose a major risk to infants. However, their limited data (evaluating only 10 women) show that the milk of some women may not supply infants with adequate iodide and they suggest that it may be important to base risk assessments for perchlorate exposure on

the iodide to perchlorate ratio or the ratio of iodide to a "selectively-weighted sum of iodide uptake inhibiting agents."

Blount and Valentín-Blasini (2006) developed a sensitive and selective method for quantifying iodide, perchlorate, thiocyanate, and nitrate in human amniotic fluid. The analytical limit of detection for perchlorate was calculated to be 0.020 µg/L. Samples of amniotic fluid at 15 to 20 weeks gestation were collected from 48 healthy women in an Eastern U.S. city for analysis. Perchlorate was found in all samples tested and exhibited a log-normal distribution. The perchlorate concentrations ranged from 0.057 to 0.71 µg/L with a median value of 0.18 µg/L.

12.4 Status of the Preliminary Regulatory Determination

At this time, the Agency is not making a preliminary regulatory determination for perchlorate. The Agency believes that additional information is needed on the sources of human exposure if it decides to base its determination regarding health risk reduction potential on a health reference level (HRL) derived from the RfD and the relative source contribution (RSC) for drinking water. Under this approach, the Agency would use the RfD and RSC to estimate an HRL and then use this HRL as a benchmark against which to conduct an evaluation of the occurrence data. In conducting such an assessment for the 6 non-carcinogens undergoing regulatory determination at this time, EPA used a 20 percent RSC, which is the lowest and most conservative RSC used to estimate an HRL. Since the initial screening of the occurrence data against the HRL resulted in a preliminary negative determination, the Agency found that it was not necessary to further evaluate the RSC for these contaminants. In the case of perchlorate, the Agency is not at the point of being able to make either a negative or a positive determination using this approach because it is not yet clear what an appropriate RSC for perchlorate is. If EPA were to use a default RSC of 20% for perchlorate, the resulting HRL would be 5 µg/L. Approximately 3.16% of the 3,858 PWSs in the UCMR 1 data set had at least one detect of perchlorate greater than or equal to 5 µg/L. Given this level of occurrence at the default-derived HRL, the Agency believes a better informed RSC and HRL would be needed to use this approach to determine whether regulation of perchlorate in drinking water presents a meaningful opportunity for health risk reduction.

Exhibit 12-3 shows the number of systems and population served that would exceed the HRL under various RSC scenarios and the sensitivity of this estimate to relatively small changes in the estimated RSC. For example, increasing the RSC from 20 to 30 percent would lower the estimated number of systems impacted by about a third, and the estimated population served by about half. Hence, the choice of an appropriate RSC and resulting HRL could impact EPA's determination of whether regulation of perchlorate represents a meaningful opportunity for health risk reduction if it uses this approach.

EPA recognizes that system-level population estimates shown in Exhibit 12-3 may be conservative because some systems have multiple entry points to the distribution system and not all entry points had a positive detection for perchlorate in the UCMR 1 survey. Hence, to derive a less conservative population estimate (last column in Exhibit 12-3), EPA assumed that the population for each system is equally distributed over all of the entry (or sampling) points and

estimated a population-served value based on entry points that had at least 1 analytical detection for perchlorate at levels greater than each of the HRL thresholds.

Exhibit 12-3: UCMR 1 Occurrence and Population Estimates for Perchlorate at Various HRL Thresholds

RSC Scenarios	Estimated HRL Thresholds Based on Various RSC Scenarios ^b	PWSs with at Least 1 Detection > Threshold of Interest	PWS Entry or Sample Points with at Least 1 Detection > Threshold of Interest ^c	Population Served by PWSs with at Least 1 Detection > Threshold of Interest ^d	Population Estimate for Entry or Sample Points Having at Least 1 Detection > Threshold of Interest ^e
20%	5 µg/L	3.16 % (122 of 3,858)	1.88 % (281 of 14,984)	14.6 M	4.0 M
30%	7 µg/L	2.13 % (82 of 3,858)	1.14 % (171 of 14,984)	7.2 M	2.2 M
40%	10 µg/L	1.35 % (52 of 3,858)	0.65 % (97 of 14,984)	5.0 M	1.5 M
50%	12 µg/L	1.09 % (42 of 3,858)	0.42 % (63 of 14,984)	3.6 M	1.2 M
60%	15 µg/L	0.80 % (31 of 3,858)	0.29 % (44 of 14,984)	2.0 M	0.9 M
70%	17 µg/L	0.70 % (27 of 3,858)	0.24 % (36 of 14,984)	1.9 M	0.8 M
80%	20 µg/L	0.49 % (19 of 3,858)	0.16 % (24 of 14,984)	1.5 M	0.7 M
100%	25µg/L	0.36 % (14 of 3,858)	0.12 % (18 of 14,984)	1.0 M	0.4 M

Footnotes:

a. These data represent summary statistics for the 3,858 public water systems that have sampled for perchlorate as a part of the UCMR 1 survey.

b. HRL threshold = [(RfD of 0.0007 mg/kg/day x 70 kg BW for pregnant female) / (2 L DWI)] x the RSC scenario. Each HRL threshold value is converted from mg/L to µg/L units and then rounded to the nearest whole number.

c. The entry/sample-point-level population served estimate is based on the system entry/sample points that had at least 1 analytical detection for perchlorate greater than the HRL threshold of interest. The UCMR 1 small system survey was designed to be representative of the nation's small systems, not necessarily to be representative of small system entry points.

d. The system-level population served estimate is based on the systems that had at least 1 analytical detection for perchlorate greater than the HRL threshold of interest.

e. Because the population served by each entry/sample point is not known, EPA assumed that the total population served by a particular system is equally distributed across all entry/sample points. To derive the entry/sample point-level population estimate, EPA summed the population values for the entry/sample points that had at least 1 analytical detection greater than the threshold of interest.

Exhibit 12-3 also includes information on the effects of using an RSC of 100% (that is, using an HRL set at the drinking water equivalent level or DWEL of 24.5 µg/L, rounded to a whole number). Crawford-Brown *et al.* (2006), in an estimate of risk variability from perchlorate exposure through community water systems, noted that the subjects in the original 2002 Greer *et al.* study (on which the RfD of 0.0007 mg/L was based) presumably had other sources of perchlorate exposure outside of the study and suggested that it may be appropriate to view their results as reflecting the effects of *incremental* exposure to perchlorate above the background levels already in food and water rather than the effects of *total* exposure, as is implicitly assumed when the HRL is derived using an RSC to account for other sources of exposure. Use of an RSC to derive the HRL is clearly appropriate when the RfD or cancer slope factor is derived from animal studies with carefully controlled exposure. Crawford-Brown *et al.* suggest, however, that an RSC is not necessary for perchlorate because there is no reason to assume that the background exposure of the study subjects was different than that of the general population. EPA notes that the sample size in the Greer study was small and EPA is not aware of data on their background exposure to perchlorate or how representative it may be.

While several States have recommended guidelines or public health goals for perchlorate, EPA recognizes that at least 1 State, Massachusetts⁷, has already promulgated a final drinking water standard for perchlorate, that other States may set drinking water standards in the future, and that these standards could impact national occurrence estimates once these standards are fully implemented.

12.5 Potential Options for Characterizing Perchlorate Exposure and Proceeding with the Preliminary Regulatory Determination for Perchlorate

While the Agency recognizes that food and other pathways may be important sources of perchlorate exposure, the Agency believes the currently available food data (summarized in section 12.3.4) are inadequate to develop a better informed RSC (and HRL). First, some of the existing data are limited in their sample numbers, geographic coverage, and analytical method adequacy. Second, the current studies provide little or no data for several food groups (e.g., meat, poultry, fish, eggs, root and tuber vegetables, brassica vegetables, bulb vegetables, tree fruits, legumes, and cereal grains) that account for about half of the diet (by mass) for females of reproductive age (mid-teens to mid-forties).

This section presents data EPA might use to estimate an RSC based on food-borne exposure as well as on several other options that the Agency is considering to better characterize perchlorate exposure and assist the Agency in making its regulatory determination for perchlorate. These options could serve as a supplement or an alternative to developing an HRL based on a better informed RSC derived from food concentration and consumption data. Specifically, urine biomonitoring data could be used to estimate perchlorate exposure. If the Agency decides to use any of the approaches discussed in section 12.5.2, EPA will need to determine what statistics (e.g., mean, median, percentile, etc.) are most appropriate for

⁷ Massachusetts promulgated a final drinking water standard of 2 µg/L for perchlorate on July 28, 2006. For more information about the final standard, see <http://www.mass.gov/dep/public/press/pchl0706.htm> (MA DEP, 2006).

consideration in a regulatory determination. The Agency will also conduct a peer review, as appropriate, of any new methodology it decides to use.

12.5.1 Use of Food Concentration and Consumption Data to Estimate an RSC

In the past, the Agency has relied on dietary exposure information from the FDA Total Diet Study (TDS) to determine the RSC allowed for drinking water and to set health goals (i.e., Maximum Contaminant Level Goals) for several inorganic compounds (e.g., antimony, cadmium, chromium, and selenium). Under the TDS, foods are sampled at retail outlets, prepared as they would be consumed, and analyzed for a variety of analytes (e.g., nutrients, pesticides, industrial chemicals). Approximately 280 foods, covering a broad spectrum of the diet, are currently sampled in each sampling event. Sampling events (known as “market baskets”) occur about 4 times per year, with each event being confined to 1 of the 4 regions of the country. The dietary intake of the analyzed compounds can be calculated for the U.S. population by multiplying the concentrations found in TDS foods by the consumption amounts for each food. FDA compiles food consumption amounts for the total U.S. population by gender and by age group⁸.

FDA is including perchlorate as an analyte in the 2006 TDS. EPA believes that a comprehensive dietary intake estimate for perchlorate will be useful in evaluating dietary exposure relative to drinking water. When sufficient quantitative exposure data are available (such as the data published by FDA in conjunction with the TDS), EPA can use the procedure used previously for several regulated inorganic compounds (i.e., chromium and selenium) to calculate the relative source contribution for perchlorate. In these cases where dietary intake values were available, EPA subtracted the dietary intake value from the Drinking Water Equivalent Level DWEL and used the remainder as the allowance for water. This procedure ensures that total exposure does not exceed the RfD.

12.5.2 Use of Urinary Biomonitoring Data to Evaluate Exposure to Perchlorate

Researchers at CDC’s National Center for Environmental Health (NCEH) have conducted a large national study of total perchlorate exposure through analysis of urine samples collected for NHANES 2001-2002 (Blount *et al.*, 2006b and 2006c). The use of urinary perchlorate excretion to estimate perchlorate exposure has been demonstrated in Valentín-Blasini *et al.* (2005), Téllez *et al.* (2005), and Blount *et al.* (2006c). While this would be the first time the Agency has used biomonitoring data to assist EPA in making a preliminary regulatory determination for a Contaminant Candidate List (CCL) contaminant, the Agency believes that estimating perchlorate exposure among large populations using urinary perchlorate excretion data may be appropriate for the following reasons:

- Perchlorate is not metabolized in the body and is excreted unchanged primarily via the renal pathway (Merrill *et al.*, 2005),
- Perchlorate does not bioaccumulate, that is, it is excreted essentially completely (Merrill *et al.*, 2005),

⁸ Information about FDA’s TDS design, food list, analytes, and analytical results can be found at www.cfsan.fda.gov/~comm/tds-toc.html. (FDA, 2006)

- Perchlorate has a short half-life in the human body (approximately 8 hours), simplifying the estimation of daily exposure (Greer *et al.*, 2002), and
- A methodology exists that allows estimation of daily perchlorate intake from all sources (e.g., water, food) using standard creatinine adjustment factors to account for variations in urine concentration (Mage *et al.*, 2004).

The Agency could use the 2001-2002 NHANES urine data in several ways as described in the following paragraphs.

One potential approach is to use the 2001-2002 NHANES urine data to determine directly whether regulation of perchlorate in drinking water presents a meaningful opportunity for health risk reduction. More specifically, we could use the urine data (as in Blount *et al.*, 2006b and c) to evaluate whether total exposure from food and water is likely to result in an appreciable risk of adverse health effects for the U.S. population. If the Agency concluded that total exposure, as estimated from the urine data, does not pose an appreciable risk, even at the upper end of the exposure distribution, then it would follow logically that reducing this exposure by regulating drinking water would not present a meaningful opportunity for health risk reduction. As summarized previously, Blount *et al.* (2006c) estimated a median total daily perchlorate dose for adults of 0.066 $\mu\text{g/kg/day}$ (about one tenth of the RfD) and a 95th percentile dose of 0.234 $\mu\text{g/kg/day}$ (about one third of the RfD). Only eleven adults (0.7%) had an estimated dose in excess of the RfD (0.7 $\mu\text{g/kg/day}$).

EPA could also use the 2001-2002 NHANES urine data to qualitatively evaluate the importance of the water contribution to overall exposure. For this approach, the Agency could merge data from the 2001-2002 NHANES and UCMR 1 and compare the total perchlorate exposure values (based on the urine data) for the population of individuals whose drinking water contains perchlorate at various concentration levels, ranging from non-detect to the upper end of the occurrence distribution. The intent of this analysis would be to permit the Agency to determine whether total perchlorate exposure (as measured in urine) is meaningfully correlated with concentrations in local public drinking water supplies, though EPA would only use these results qualitatively because it is not possible to match up individual urine samples with individual drinking water exposures. However, the results could be useful in determining at least qualitatively the potential significance of drinking water exposure for total exposure. If there were not a significant correlation between public water system perchlorate occurrence and individual exposure as measured through biomonitoring, this might suggest that there is not a meaningful opportunity for health risk reduction through regulation of drinking water.

The Agency could also potentially use the 2001-2002 NHANES urine data to derive an RSC to use for drinking water. This could potentially be done in several different ways as follows.

Use of Urinary Biomonitoring Total Exposure Value to Estimate an RSC

One possible approach to estimating an RSC for water would be to use the urine data to estimate total perchlorate exposure, then subtract this exposure value from the reference dose and allow the remainder as the exposure limit for water. The allowed remainder divided by the RfD would be the RSC for drinking water. This approach would yield a conservative RSC value

because the exposure used to represent food would actually correspond to both food and drinking water exposure, whereas, if it were possible to estimate the exposure from food alone, the relative amount allowed for water would be larger (resulting in a higher RSC and higher health reference value). As discussed in Section 12.3.5, above, Blount *et al.* (2006c) estimated a total daily perchlorate dose for adults from urine data and found a median dose of 0.066 $\mu\text{g/kg/day}$ (about one tenth of the RfD) and a 95th percentile of 0.234 $\mu\text{g/kg/day}$ (about one third of the RfD). If EPA were to use the estimated 95th percentile total dose from the Blount study as if it represented the exposure from food alone, this would suggest a residual screening-level RSC of about 70% allocated to water. One possible limitation of this approach is that the Blount study estimates exposure for adults only. Therefore, an RSC developed based upon this data would not necessarily be representative of children.

Use of the Urine Data and UCMR 1 to Deduce Exposure from Other Sources and Derive the RSC

Alternately, for those NHANES survey subjects served by public drinking water systems with positive detections for perchlorate (based on UCMR 1), EPA could estimate the expected perchlorate dose contributed by drinking water (using individual water consumption data from the NHANES survey combined with UCMR 1 data for the area in which they live) and subtract it from the total perchlorate dose (based on urinary perchlorate excretion data) to calculate the amount contributed by food. Subtraction of this calculated food contribution from the RfD would yield the amount allowed for drinking water, which could be divided by the RfD to calculate an RSC. One limitation of this methodology would be the assumption that subjects in the NHANES study are uniformly consuming drinking water that contains perchlorate at the concentration indicated in the UCMR 1 data for their area.

Use of Urinary Biomonitoring Data from Exclusive Bottled Water Drinkers to Estimate an RSC

The 2001-2002 NHANES data includes urinary perchlorate data for populations who exclusively drink bottled water. As noted in section 12.3.4, above, FDA (2004) tested 51 samples of bottled water from 34 distinct sources in 12 states and detected perchlorate in 2 samples (at levels of 0.56 $\mu\text{g/L}$ and 0.45 $\mu\text{g/L}$). These levels are well below the MRL for the UCMR 1 data and would not contribute significant amounts of perchlorate relative to the RfD. If the population of exclusive bottled water drinkers is sufficiently representative of the U.S. population, these data potentially could be used to estimate the contribution of perchlorate exposure coming from food and allow the Agency to estimate an RSC for drinking water. The RSC value could be derived by subtracting the estimated perchlorate exposure for exclusive bottled water drinkers from the RfD of 0.0007 mg/kg/day , using the remainder as the allowance for drinking water. One limitation of this methodology is that the perchlorate concentration of the bottled water used by this NHANES population is not known. Hence, we would have to assume that the bottled water concentration data collected by FDA (2004) is representative of the perchlorate concentration in the bottled water used by the NHANES exclusive bottled water population. Another limitation of this approach is that it would not subtract out the fraction of the drinking water intake that comes from water used for cooking purposes (since bottled water is probably not used by most subjects in cooking and household food preparation). It would thus

produce a conservative (health protective) estimate of the RSC as it would overestimate the fraction of total exposure coming from food.

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